PREDICTORS AND MANAGEMENT OF NEUTROPENIA AMONG PAEDIATRIC PATIENTS WITH HAEMATOLOGICAL MALIGNANCIES AT KENYATTA NATIONAL HOSPITAL

Patrick Muthini (B. Pharm)

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Name of Student	Patrick Muthini John
Registration Number	U56/37595/2020
Faculty/School/Institute	Faculty of Health Sciences
Department	Pharmacology, Clinical Pharmacy and Pharmacy Practice
Course Name	Master of Pharmacy in Clinical Pharmacy
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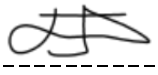
Signature: 

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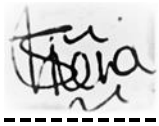
SUPERVISOR'S APPROVAL

This dissertation has been submitted for review with our approval as University of Nairobi supervisors.

1. Dr. Peter N. Karimi, PhD
   Senior Lecturer
   Department of Pharmacology, Clinical Pharmacy and Pharmacy Practice
   Faculty of Heath Sciences
   University of Nairobi

   Signature:  **Date:** **20/11/2023**

2. Dr. Irene Weru, MPharm
   Senior Specialist Pharmacist
   Kenyatta National Hospital

   Signature:  **Date:** **20/11/2023**

DEDICATION

This dissertation is dedicated to beloved wife Dianah Gachunku and our cherished daughters, Tiffany Melissa and Daffney Mutheu for their unending support and encouragement throughout my life in the university.

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ABBREVIATIONS AND ACRONYMS

ALL:	Acute Lymphoblastic Leukaemia
AML:	Acute Myeloid Leukaemia
ANC:	Absolute Neutrophil Count
ASCO:	American Society of Clinical Oncology
BEACOPP:	Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine and Prednisone.
BMI:	Body Metabolic Index
BSA:	Body Surface Area
CIN:	Chemotherapy Induced Neutropenia
CISNE:	Clinical Index of Stable Febrile Neutropenia
CLL:	Chronic Lymphoblastic Leukaemia
CML:	Chronic Myeloid Leukaemia
COPD:	Chronic Obstructive Pulmonary Disease
ECOG:	Eastern Cooperate Oncology Group
EGFR:	Estimated Glomerular Filtration Rate
ESMO:	European Society of Medical Oncology
FN:	Febrile Neutropenia
G-CSF:	Granulocyte Colony Stimulating Factor
HL:	Hodgkin Lymphoma
KNH:	Kenyatta National Hospital
MASCC:	Multinational Association for Supportive Care in Cancer
NCCN:	National Comprehensive Cancer Network
NCI:	National Cancer Institute
NF:	Neutropenic Fever
NHL:	Non-Hodgkin's Lymphoma
PI:	Principal Investigator

OPERATIONAL DEFINITIONS

Chemotherapy Induced Neutropenia (CIN)	Absolute Neutrophil Count ≤ $1.5*10^9$/l following administration of antineoplastics
Febrile Neutropenia (FN)	Defined as a single oral temperature of ≥38.3°C (100º F) or a temperature of ≥ 38.0°C (100.4º F) that persist for ≥ 1 hour and a profound neutropenia an absolute neutrophil count (ANC) of $<0.5 \times 10^9$/l, or expected to fall below 0.5×10^9/l.
Baseline ANC	ANC value before initiating the first cycle of chemotherapy
Chemotherapy dose delay	Delay of planned chemotherapy for more than or equal to seven days
Mild Neutropenia	ANC levels between 1.0- $1.5*10^9$/l
Moderate Neutropenia	ANC levels between 0.5-$1.0*10^9$/l
Severe Neutropenia	ANC levels $<0.5 *10^9$/l

ABSTRACT

Background: Neutropenia is a common complication of chemotherapy treatment in patients with malignancies which requires adequate prevention, urgent diagnosis, and appropriate intervention. It is associated with significant morbidity, mortality, and increased healthcare expenditure. There is scanty literature about the burden as well as predictors of neutropenia among paediatric patients with haematological malignancies.

Objective: To evaluate the predictors and management of neutropenia among paediatric patients with haematological malignancies at Kenyatta National Hospital.

Methodology: A cross-sectional study was conducted on paediatric cancer patients aged between 0-15 years who were attended at Kenyatta National Hospital between January 2019 and June 2022. 143 participants were selected using simple random sampling. Data was collected with a pretested well-structured abstraction tool and stored in a password protected Microsoft Excel Spreadsheet version 2010. It was then be analysed using STATA version 15.1. Chi square test was used to determine presence of significant association between neutropenia and the predictors. Binary and multivariate logistic regression was conducted to deduce any association between presence of neutropenia and the independent variables. The p-value was set at 0.05.

Results: A total of 143 haematological cancer patients at Kenyatta National Hospital were evaluated. From bivariate analysis, neutropenia was associated with: ALL, HL, the L2 morphological classification of ALL, induction, consolidation and maintenance treatment phases, heart failure and thrombocytopenia comorbidities as well as use of the combined regimen of 6-mercaptopurine, methotrexate, vincristine, doxorubicin, and cyclophosphamide. Independent predictors of neutropenia were the induction and consolidation phases of treatment. Of the 111 (77.6%) patients who had neutropenia, 17 (15.6%) developed fever. The neutropenia took more than 7 days to resolve in 71 (63.4%) patients.

Conclusion: Induction and consolidation phases of treatment were significantly associated with chemotherapy induced neutropenia. The use of GCSF, combination of antibiotics or chemotherapy deferment were employed in the management of febrile neutropenia.

Recommendation: Prospective studies should be conducted to unravel other determinants of neutropenia among paediatric haematological cancer patient

CHAPTER ONE: INTRODUCTION

1.1 Background

Cancer is among the top causes of mortality worldwide. A global estimate of 19,300,000 new cancer cases and ten million cancer deaths or nearly one in every six deaths in 2020 was recorded with a projection of 28,400,000 new cancer cases by 2040 (1). Several developing and underdeveloped countries have shown upward trajectory of cancer risks that were known to prevail in developed countries such as consumption of unhealthy diets, excessive body weight, sedentary lifestyle with increased inactivity as well as smoking (2). This has led to shifting of the global cancer burden to less developed countries accounting for 57% of incident cases and 65% of mortalities globally (3).

The extend of worldwide burden of childhood cancer is poorly documented to date. Childhood cancers have been on the increase globally with approximately 400,000 children aged between zero and 19 years being diagnosed with malignancy every year.

The epidemiology of childhood cancers is still poorly studied especially in Sub-Saharan Africa and may be underestimated as a result of poor diagnosis, lack of access to dedicated paediatric cancer centers, too few paediatric oncology specialists as well as lack of well-equipped cancer registries (4–6). Adults are more likely to develop solid tumors while children and adolescents less than 20 years tend to develop haematological malignancies. The common haematological malignancies include Non-Hodgkin's Lymphoma, Acute Myeloid Leukaemia, Acute lymphoblastic Leukaemia, Chronic Myeloid Leukaemia, Hodgkin's Lymphoma and Chronic Lymphoblastic Leukaemia. Leukaemia predominates the childhood cancers. An Indian study shows that it accounts for 40-50% while lymphomas account for 15-20% of the cancers (7). Other studies have shown the prevalence of leukaemia to be 30-50% further supporting the high rates (8–10).

Cancer management modalities include surgery, radiotherapy, and chemotherapy. Surgery and radiotherapy are used in management of localized tumors while chemotherapy alone or concurrent use of chemotherapy, surgery and radiotherapy is commonly used in management of metastatic tumors. Other newer treatment modalities include immunotherapy, bone marrow transplant, gene therapy and use of biological modifiers (11,12). Advancement in cancer management has gained

substantial progress leading to introduction of more precise, minimally invasive surgeries with molecular imaging support as well as more targeted radiotherapy. Chemotherapy currently has better dosing regimens, neoadjuvant and adjuvants have been discovered and there is more justification for combined therapy.

Despite the achievements in cancer management, chemotherapy induced adverse effects remain a great challenge (13). Some of these toxicities are selective to particular agents while others are general for all anticancer agents. Short term adverse effects of chemotherapy range from nausea and vomiting, local irritation, allergic reactions, and hypotension while the long-term adverse effects include bone marrow suppression, alopecia, and secondary malignancies amongst many others.

Neutropenia, a consequence of bone marrow suppression is a significant and most frequent complication of cancer treatment. It affects cancer patients in several ways such as increasing risk to life threatening viral, bacterial, parasitic, or fungal infections. These infections increase mortality rate, hospitalizations, and cost of care. In addition, neutropenia leads to treatment interference which includes reduction of dose intensity, change of regimen to less effective regimen or even more toxic regimen. Finally, neutropenia leads to treatment discontinuation that reduces cure rate and survival (14). Understanding the prevalence, predictors and management of chemotherapy induced neutropenia therefore is very key to helping reduce the morbidity and mortality associated with it.

1.2 Problem statement

Neutropenia among cancer patients receiving antineoplastics occur mainly due to the myelosuppressive nature of most of the anticancer drugs. The burden of neutropenia among paediatric patients with blood cancers has not been documented to date. The only studies available have focused on prevalence of neutropenia in solid tumors (15). The prevalence is postulated to be higher in haematological malignancies because in addition to the cytotoxic chemotherapy, the disease condition itself is myelosuppressive and paediatrics have underdeveloped immunity (16,17).

Similarly, various studies have documented determinants of neutropenia both in solid tumors and haematological malignancies. These determinants include age, gender, body surface area, nutritional status, choice of chemotherapy, type of cancer, prophylactic use of G-CSF, number of chemotherapy cycles used, abnormal renal and hepatic functions, baseline low white blood cells, previous exposure to radiotherapy and use of immunosuppressive drugs like steroids (18–23). However, very few studies have been done in haematological malignancies globally and none has been done in Kenyan setting.

Even though there are several guidelines and protocols at institutional level, nationally and globally, there remains a gap in prophylaxis and management of febrile neutropenia (24). This is probably due to the presence of many conflicting guidelines and lack of consensus on risk classification based on the available clinical evidence (25).

The predictors of neutropenia have not been investigated at KNH despite it being common among patients on chemotherapy. The management of this condition is not optimal. These observations necessitate a study to be carried out so that the prevalence and consequences of neutropenia may be mitigated.

1.3 Justification of the study

There have been very few studies if any globally on prevalence of neutropenia and predictors of CIN among paediatric patients with haematological cancers.

Additionally, there is no local study documenting the predictors and prevalence of CIN among paediatric patients with haematological malignancies. The only available studies have focused on management of neutropenia in paediatrics (26) and adults (27,28). This establishes a need to have a rich pool of locality data on the predictors and management strategies of neutropenia in haematological malignancies that suites the paediatric populations. The findings of this study on the management strategies of neutropenia will add to the existing knowledge.

1.4 Research questions

1. What is the prevalence of neutropenia among paediatric patients with haematological malignancies at KNH?
2. What are the predictors of neutropenia among paediatrics patients with haematological malignancies at KNH?
3. What are the management strategies of neutropenia among paediatric patients with haematological malignancies at KNH?

1.5 Objectives

1.5.1 Main objective

To evaluate the predictors and management of neutropenia among paediatric patients with haematological malignancies receiving antineoplastics at KNH.

1.5.2 Specific objectives

1. To determine the prevalence of neutropenia among paediatric patients with haematological malignancies at KNH.
2. To analyse the predictors of neutropenia among paediatric patients with haematological malignancies at KNH.
3. To evaluate the management strategies of neutropenia among paediatric patients with haematological malignancies at K

CHAPTER TWO: LITERATURE REVIEW

2.1 Introduction

This chapter reviews the prevalence of neutropenia in paediatrics with haematological malignancies. It also reviews the current literature on risk factor of CIN and its management strategies.

2.2 Prevalence of neutropenia

Neutropenia is the decrease in the circulating ANCs which have a primary role in body defence against infectious pathogens. It can be congenital or acquired. The most common causes of acquired neutropenia include viruses, medications such as cytotoxics and steroids, or autoimmune diseases. The documented pathologic mechanisms of neutropenia include decreased bone marrow production, sequestration of neutrophils, and increased destruction of circulating neutrophils. It may be characterized as mild, moderate, or severe.

Neutropenia significantly increases morbidity and mortality among cancer patients undergoing chemotherapy. Febrile neutropenia recognized as a medical emergency contributes to an increment in mortality and hospitalizations (29–31). The high mortality and morbidity is partially because of the quantitative relationship between circulating neutrophils and infections with pathogens such as bacteria, viruses, fungi and parasites (32). This can even progress to life threatening sepsis.

NF may necessitate dose reductions, chemotherapy dose delay, discontinuation or use of alternative less toxic but less effective regimens. The sub optimal levels of cytotoxics compromise their therapeutic efficacy further leading to poor outcomes.Management of the infections and the other complications that are as a consequence of FN have an add-on effect to the healthcare costs whether directly or indirectly (31).

Several studies have been done to document burden of neutropenia in solid tumors unlike in haematological cancers. One study reported an incidence of 2.0% in breast cancer and 12.0 % in lymphomas after first two cycles of chemotherapy (33). The incidence in lymphomas agrees with a six year Thai retrospective cohort study done on haematological malignancies which reported an incidence of 14.9% (34).

A study done at KNH reported a 43.7% incidence of neutropenia by second cycle of chemotherapy in both NHL and breast cancer (35). However, very few of these cases (2%) progressed to febrile neutropenia.

2.3 Predictors of neutropenia

The predictors of neutropenia categorized according to factors related to either the patient or the treatment. Patient factors include patient age, weight and its related parameters such as BSA and BMI, gender, type of malignancy, and comorbidities such as renal, endocrine, cardiovascular, liver and nutritional diseases. Previous chemotherapy, radiotherapy and immunosuppressive therapy are also implicated.

Advanced age especially ≥65 years increases the risk of neutropenia (20,23,36–40). This is probably due to immune senescence (41). This population is also associated with reduced bone marrow, renal and liver functions (41). However, since this study is based on paediatric population, this risk may not be well proven as per the available literature.

Dosing of chemotherapy is majorly based on BSA. BMI is directly proportional to weight (kg). Bigger Body Surface Area (BSA) of $>2m^2$ and lower BMI predispose patients to NF (38,39). Similarly increased weight and by extension increased BMI is therefore protective against neutropenia (40). However, other studies have reported contrasting findings that decreased BSA is a predictor of FN (42,43).

Male gender has been reported in lung cancer as a risk factor of neutropenia (21). However, this is inconsistent with other studies done on NHL (44) and small cell lung cancer (45) where the females are reported to be more predisposed to CIN.

Haematological malignancies are more associated with both neutropenia and febrile neutropenia compared with solid tumors. A study by Klastersky found out that FN develops in upto 50% of patients with solid tumors and >80% of patients with blood cancers during chemotherapy cycles (46). This is because the malignancies by themselves create inflammatory state whereby, production of both mature and progenitor immune cells is stimulated by the released cytokines. The cytokines also promote differentiation and maturation of the granulocytes. In some cases, the tumor cells directly replace the neutrophils in the bone marrow. A significant difference is also seen within the haematological malignancies. For instance, one study reported a neutropenic

incidence of 20% in Hodgkin lymphoma and more than 80% in Chronic Myeloid Leukaemia (CML) (42). A local study done at KNH reported a baseline prevalence of 80% in ALL among paediatrics (47).

Most of the chemotherapeutic agents are detoxified in the liver and antineoplastics are not exceptional. Impaired liver function as demonstrated by either an increased level of baseline bilirubin, decreased serum albumin to ≤ 3.5g/dl or increased aspartate transaminases (37,39,40) is a risk for neutropenia due to the bioaccumulation of myelotoxic antineoplastics.

Drugs like cyclophosphamide are excreted via the renal system. Reduced renal function either independently, as a result of the malignancy or nephrotoxic agents leads to bioaccumulation of the drugs further predisposing the patient to myelosuppression (23,44). Adriana Stryczyńska-Mirocha et al.'s research revealed a correlation between mild impairment in kidney function and the occurrence of neutropenia in individuals undergoing cancer treatment (48). Similarly, comorbidities such as, hypertension, heart diseases, Chronic Obstructive Pulmonary Disease (COPD) and diabetes increase the risk of CIN via unclear mechanisms (49–51).

Majority of cancer patients are malnourished, and this interferes with their immunity predisposing them to infections. Malnutrition is therefore a direct cause as well as a risk factor of febrile neutropenia (52). Repeated exposure to antineoplastic agents leads to chronic suppression of the bone marrow. This results in a chronic hypoplasia with a permanent decrease in cell counts as demonstrated in a study on multivariate analysis of FN occurrence in NHL (40).

Radiotherapy is one of the management techniques highly used for solid tumors especially at the localized stage. It can cause direct apoptosis and failure of the bone marrow hence contributing to cytopenias. The association between previous radiotherapy and neutropenia has been shown in various studies on solid tumors (21,38).Use of drugs such as corticosteroids is a well-recognized cause of neutropenia. A retrospective study on predictors of neutropenia in patients with oesophageal cancer undergoing treatment with antineoplastics reported steroid use as an independent risk factor of neutropenia (22). There are various treatment related determinants of occurrence of neutropenia which include type of chemotherapy, doses of the chemotherapy used, number of chemotherapy cycles and prophylactic use of G-CSF.

Cancer treatment with most traditional antineoplastic agents have a myelotoxic or myelosuppressive effect on the bone marrow. This causes cytopenias across all the cellular lineages. Chemotherapy-related myelotoxicity and myelosuppression is dose dependent. For instance, increased risk of neutropenia has been shown in patients receiving increased-dose of BEACOPP compared to the standard dose of BEACOPP in management of Non-Hodgkin's Lymphoma (53).

First and second chemotherapy cycles are independently associated with Febrile neutropenia occurrence (21,34,35). The incidence of subsequent neutropenia decreases with increased number of cycles received (21).G-CSF significantly decrease the occurrence and hazard of the mortality associated with FN especially when used in high risk subgroups such as patients with suboptimal performance status, those receiving intensive chemotherapy regimens, patients with ≥65 years, patients with reduced liver and renal functions or patients who are immunodeficient (29,34,36,40).

2.4 Chemotherapeutic regimens implicated in neutropenia

Chemotherapy regimens have different levels of risk to FN depending on the degree of myelosuppression. Single-agent cytotoxic agents used such as docetaxel, etoposide, doxorubicin, cyclophosphamide as well as their combinations are myelosuppressive and therefore are frequently associated with neutropenic events (40). All regimens used in the management of AML have been linked with higher risk of CIN regardless of use of G-CSF (34).

2.5 Management strategies of febrile neutropenia

Several guidelines have several recommendations for both treatment and prophylaxis of fully diagnosed FN. However, all of them appreciate FN as an emergency requiring prompt treatment.

2.5.1 The ESMO guidelines

According to these guidelines, the suggestion to use G-CSF arises when the risk of chemotherapy-associated FN is 20% or higher or when it is 10-20% but the risk associated with other factors such as age >60 years adds to an overall risk of ≥20% (54).

Patients at low risk of neutropenia are managed as ambulatory patients using a fluoroquinolone or amoxicillin/clavulanic acid combination preferably per oral which targets both gram negative and gram-positive microbes. The high-risk patients on the other hand are treated as inpatients with antibiotic selection based on culture and sensitivity. Daily teicoplanin is highly preferred.

Antibiotics are stopped if a patient is neutropenic and afebrile for more than 48 hours and there is a negative screen for bacteria (54).

2.5.2 The American Society of Clinical Oncology Guidelines

ASCO employs either clinical judgment criteria or a MASCC score of less than 21 to categorize patients as high-risk, recommending inpatient care for this group. Conversely, patients with a score of 21 or higher are considered low risk, suggesting that they may be suitable for outpatient care. It recommends the outpatient use of both amoxicillin clavulanic acid and ciprofloxacin or moxifloxacin or Levaquin for low-risk patients without prior exposure to fluoroquinolones and IV cefepime if the patient has exposure to fluoroquinolone. The high-risk patients should receive IV antibiotics as inpatients with preferable empirical choices based on Piperacillin+ tazobactam (anaerobic cover), Meropenem (extended spectrum beta lactamase resistant cover) and Cefepime (55).

2.5.3 NCCN guidelines

In accordance with NCCN guidelines, patients are stratified into low or high-risk categories based on a combination of factors, incorporating evaluations of MASCC and CISNE scores (56). According to NCCN, patients identified as high risk for neutropenia are advised to receive G-CSF.

2.6 Identified gap

There is no single study that focuses on, and documents the prevalence of neutropenia among haematological malignancies in the Kenyan setting. Secondly, the studies on determinants of chemotherapy induced neutropenia are highly focused on solid cancers and the adult population and none of them has been done in the Kenyan setting. This study, therefore, aims to document the prevalence and determinants of neutropenia in haematological malignancies among the paediatric population at KNH.

2.7 Conceptual framework

This study is anchored on four areas namely, prevalence of chemotherapy induced neutropenia, determinants of neutropenia development and management strategies of CIN at KNH. The prevalence of CIN is dependent on patient and treatment related factors well as the proper management and prophylaxis of CIN. Greater prevalence can be attributed to deficiencies in treatment and prophylaxis, while, conversely, effective treatment and prophylactic measures would lead to a reduced prevalence.

From the presented literature review, neutropenia is directly caused by corticosteroid use, haematological cancers, and the use of chemotherapy, this will be controlled by limiting the study only to the patients with haematological malignancies undergoing chemotherapy. Since steroids are a cause as well as risk factor of neutropenia, patients with documented steroid use will not be excluded from the study. The conceptual framework is depicted in **Figure 2.1**.

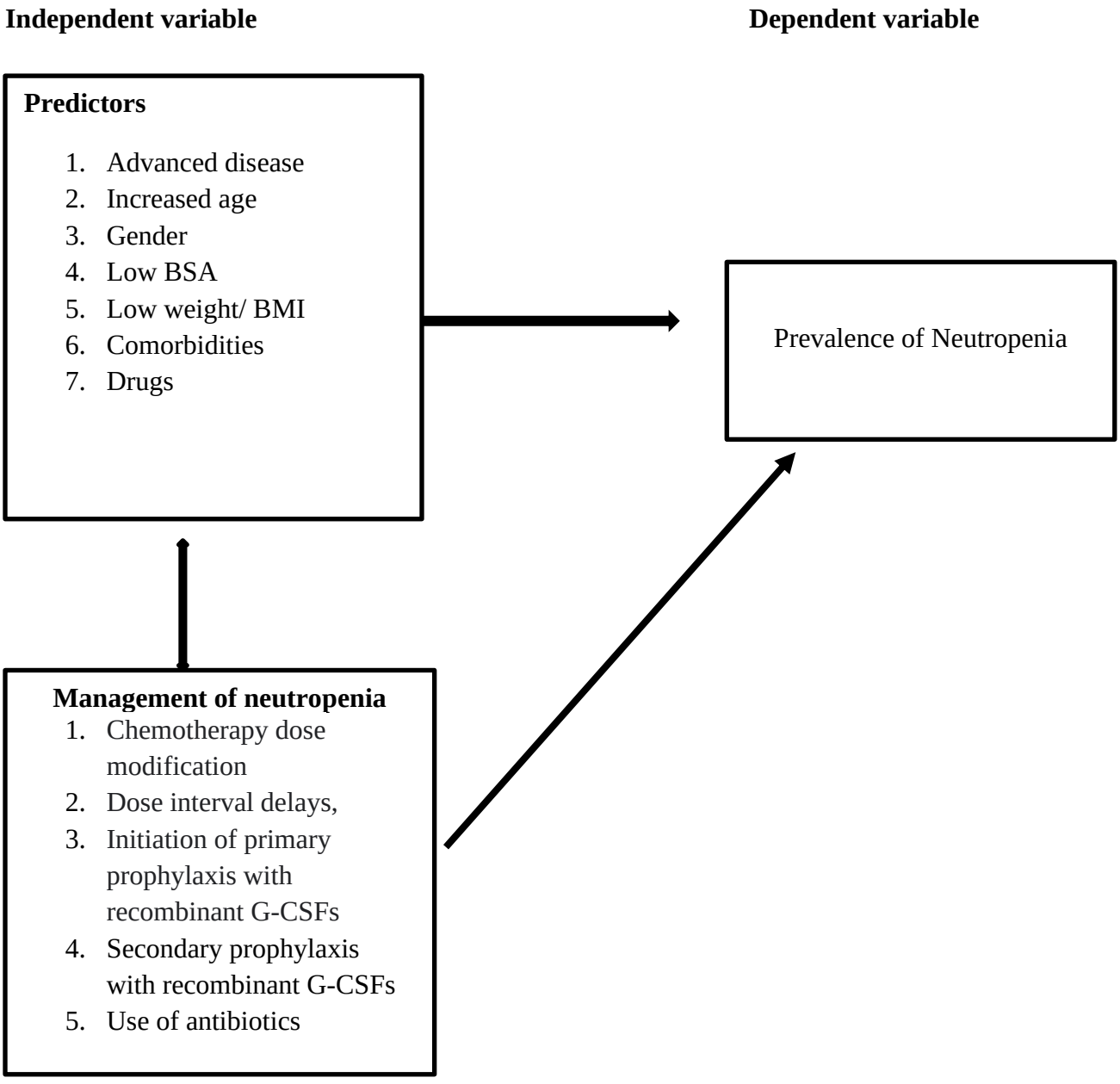

Figure 2. 1 Conceptual framework

CHAPTER THREE: MATERIALS AND METHODS

3.1: Introduction

This chapter highlights the study design, research setting, target and study population, participant eligibility, sample size calculation and sampling technique, research tools and techniques, data validity and reliability, data management and analysis as well as ethical considerations.

3.2: Study design

A cross-sectional study was conducted within a hospital environment, where medical records of children aged 0-15 years diagnosed with haematological malignancies at Kenyatta National Hospital were reviewed. This study design is relatively economical and easy to conduct. It involves definition of study population, sampling as well as recruitment of study participants, data collection and analysis, interpretation of the results and finally assessment of the potential causes of error. Data on exposure and outcome were collected simultaneously.

3.3 Research setting

The study was conducted at Kenyatta National Hospital, a level 7A government hospital which is recognized as Kenya's oldest and largest teaching and referral hospital. It's located at Nairobi, the capital city as well as the largest city in the country. Its exact location is about 3500 meters from the central business district (CBD). It has a total bed capacity of 1,800 spread over fifty wards, 22 outpatient clinics, accident, and emergency department and 24 surgical theatres. Being a public facility, it offers comprehensive cancer care at an affordable cost and has relatively sufficient number of specialists in paediatric oncology. The cancer services provide both outpatient and inpatient services including chemotherapy, hormonal therapy, immunotherapy, radiotherapy, targeted therapy, surgical treatment, and brachytherapy.

The exact study setting was within the health information management department where patient medical record files are kept. The files of interest were for patients admitted to the specialized paediatric oncology, 1E which has a capacity of a 28 beds, the paediatric oncology ward 3D which is housed within the paediatric wards to handle admitted patients for confirmed malignancies, ward 8C where paediatrics between 13 and 15 years are admitted as well as paediatric outpatient oncology clinics.

3.4 Target and study population

The target population in the study was paediatric patients with confirmed haematological malignancies. The study population involved children between 0-15 years visiting Kenyatta National Hospital with confirmed haematological malignancies and receiving chemotherapy at KNH between January 2019 and June 2022.

3.5 Inclusion and exclusion criteria

3.5.1: Inclusion criteria

Participants were included in the study if;

1. they were aged 15 years and below with confirmed haematological cancer,
2. they had received chemotherapy at KNH.

3.5.2: Exclusion criteria

Participants were excluded from the study if;

1. they had a history of allogeneic stem cell transplantation within the previous year or the neutropenia occurred immediately after stem cell transplantation
2. they had been initiated on chemotherapy at KNH but were not visiting the paediatric oncology departments for follow-up and
3. they had incomplete medical records.

3.6 Sample size determination and sampling technique

3.6.1 Sample size determination

Cochran single proportion formula for a categorical variable was applied in the calculation of the desired sample size for the study (57). According to the information obtained from the KNH records department, 772 admissions due to haematological malignancies among paediatrics aged 0-15 years were reported between January 2019 and June 2022.

$$no = \frac{z^2 * p(1-p)}{d^2}$$

Where;

No -Calculated sample size

Z -Value from standard normal distribution associated with confidence level.

P -Proportion estimate.

d -Margin of error (acceptable maximum error for the mean being estimated or how much deviation we are willing to accept). Since the outcome variable is categorical, d was set at 0.05.

A confidence interval (CI) of 95% and a standard normal distribution (Z) of 1.96 was used. The margin of error (d) was set at 0.05 as described above and since no study had been found with the prevalence of neutropenia in haematological malignancies after a thorough literature search, a prevalence of 50% was used in the sample size calculation.

$$no = \frac{1.96^2 * 0.50(1 - 0.50)}{0.05^2}$$

$$=384.16 \approx 384$$

Considering the small size of the targeted population at KNH, calculated sample size was corrected using the Cochran correction for finite populations.

$$n = \frac{no * N}{no + (N - 1)}$$

Where,

n- adjusted sample size

no- calculated sample size.

N- The approximate number of pediatric patients undergoing treatment for blood cancers at KNH was determined based on data obtained from the Health Records Department. Within the study period, records indicated that 772 patients with hematological cancers were under management.

$$n = \frac{345 * 772}{345 + (772 - 1)}$$

$$=238.66 \approx 239$$

Additional 10% of the calculated sample size was added to cater for poor quality missing or medical records;

$$N = n + {}^{10}/_{100} * n$$

$$N = 239 + {}^{10}/_{100} * 239 = 262.9 \sim 263 \text{ participants}$$

3.6.2 Sampling technique

Participants were selected using the lottery method which is an example of simple random sampling. The method ensured that a representative sample was obtained which in turn ensured those statistical indices calculated on the sample accurately represent the population parameters. It is a simple method which reduces the effects of selection bias.

A sampling frame composed of the paediatric patients with haematological malignancies who received chemotherapy at KNH was obtained from the records department. All the files were assigned chronological numbers ranging from 1 to 772 comprising the universe. The numbers were then be placed in a box and mixed after which the principal investigator picked numbers from the box until the calculated sample size was achieved. The files corresponding to the numbers picked were perused and the data abstracted accordingly.

3.7 Research instruments

A pretested, well-structured data abstraction tool (Appendix 2) was used to collect data. The data abstraction tool was prepared by reviewing different kinds of literature with aim of collecting the necessary data from the participant's medical records. Collected data included participants' demographics such as BMI, gender, age as well as body surface area. The form also collected clinical data which included: type of malignancy and staging, type of chemotherapy regimen used, and cycles or phases received so far, ANC, body temperature at the time of diagnosis of neutropenia, comorbidities and the strategy used in the management of neutropenia. The NCCN guidelines were used as a reference in the evaluation of the appropriate indications of prophylaxis and empiric antibiotic for NF. A waiver of consent was sought since the study was limited to patient medical records. An eligibility form (Appendix 1) was used to determine who will be eligible for the study.

3.8 Pretesting

The forms and procedures were pretested by the principal researcher using 5% of the sample size at KNH one month preceding the study. This then allowed detection of the inadequacy of data abstraction form. The data abstraction form was then revised as per the pre-test results. The records used during pretesting were not included in the main study.

3.9 Data Validity

The study was designed with adequate consideration of both external and internal validity with aim of allowing the inferences drawn from the sample to be generalized to the target population. Kenyatta National Hospital being a national public referral hospital that offers a wide range of cancer management services was appropriate for the study. Simple random sampling was done to ensure every participant has equal chance of being included in the study. To achieve internal validity, the principal investigator ensured that the questions are accurate after pretesting. The external validity was achieved by ensuring that the sample size was adequate, and selection was done using simple random sampling.

3.10 Reliability

To ensure reliability of the study findings, the data abstraction form was pre-tested, and review done. The research assistant used in the study was trained by the principal investigator.

3.11 Data collection techniques

The data abstractor introduced himself to the records department with a copy of the approval letter from KNH/UON- ERC as well as the administrative permissions granted by KNH and received the patient identifiers which were used in sampling. The sampled files were retrieved and subjected to the eligibility protocol. Since the study involved patient medical records, a waiver had been sought from KNH/UON- ERC. For the active patients (patients in the wards), the principal investigator introduced himself to the nursing officer in charge in the specific ward and presented the necessary documents seeking permission to access the patient files.

Participants' files were studied carefully obtaining the required data using the pretested data abstraction form (**Appendix 2**). The dash symbol (-) was employed to signify missing variables. The process of real-time data abstraction was carried out solely by the principal investigator and one research assistant. Review of active medical records was scheduled in such a way that it did

not interfere with the care the participants were receiving. At closure of each day, the lead investigator checked the data abstraction forms for completeness.

3.12 Data management and analysis

The collected data was entered in a Microsoft Excel Spreadsheet version 2010 in a csv format and stored in a password protected laptop. The stored data was exported to STATA version 15.1 for analysis (58). Continuous normally distributed variables were presented as means (sd). Categorical variables were presented using frequency distribution tables. Chi square test for independence was used to determine presence of association. Bivariate and multivariate logistic regression was done to determine the extent of association between the dependent and independent variables. The dependent variable was neutropenia while the independent variables included age, gender, BMI, BSA, type of malignancy, stage of malignancy, regimens used and comorbidities. P value of < 0.05 was considered as statically significant.

3.13 Logistical and ethical considerations

Ethical clearance for this study was granted by the KNH-UON ERC. Following this, authorization to conduct the study at KNH was sought from the KNH Research and Programs Department. Due to the retrospective nature of the study involving the review of patient medical record files, a waiver for informed consent was requested.

Patient confidentiality was maintained by ensuring the collected data did not have any direct patient identifiers such as patient name or patient hospital number. Instead, codes were generated to act as patient identifiers. The data extraction forms were locked in a secured cabinet with only the PI having access to it while the ones transferred to excel were stored in a password protected laptop accessible only to the PI. This data was only used for research purposes.

Since the participants in the wards were receiving the accepted standard of care in the hospital, there was no any alteration in the patients' treatment modality.

CHAPTER FOUR: RESULTS

4.1 Introduction

This chapter presents the findings resulting from descriptive, inferential, and exploratory analyses of the gathered data. It covers a range of aspects, including patients' sociodemographic profiles, baseline laboratory values, clinical parameters, regimens used, and the prevalence of CIN among paediatric patients with haematological malignancies at KNH from January 2019 to June 2022.

4.2 Participant selection

The statistics department detected an error that had occurred when obtaining the list of 772 participants to calculate the sample size. The system could only generate 627 records and out of these records, only 283 files were traced. 140 files failed the inclusion criteria with only 143 participants being included in the study as presented in the consort diagram in **figure 4.1**.

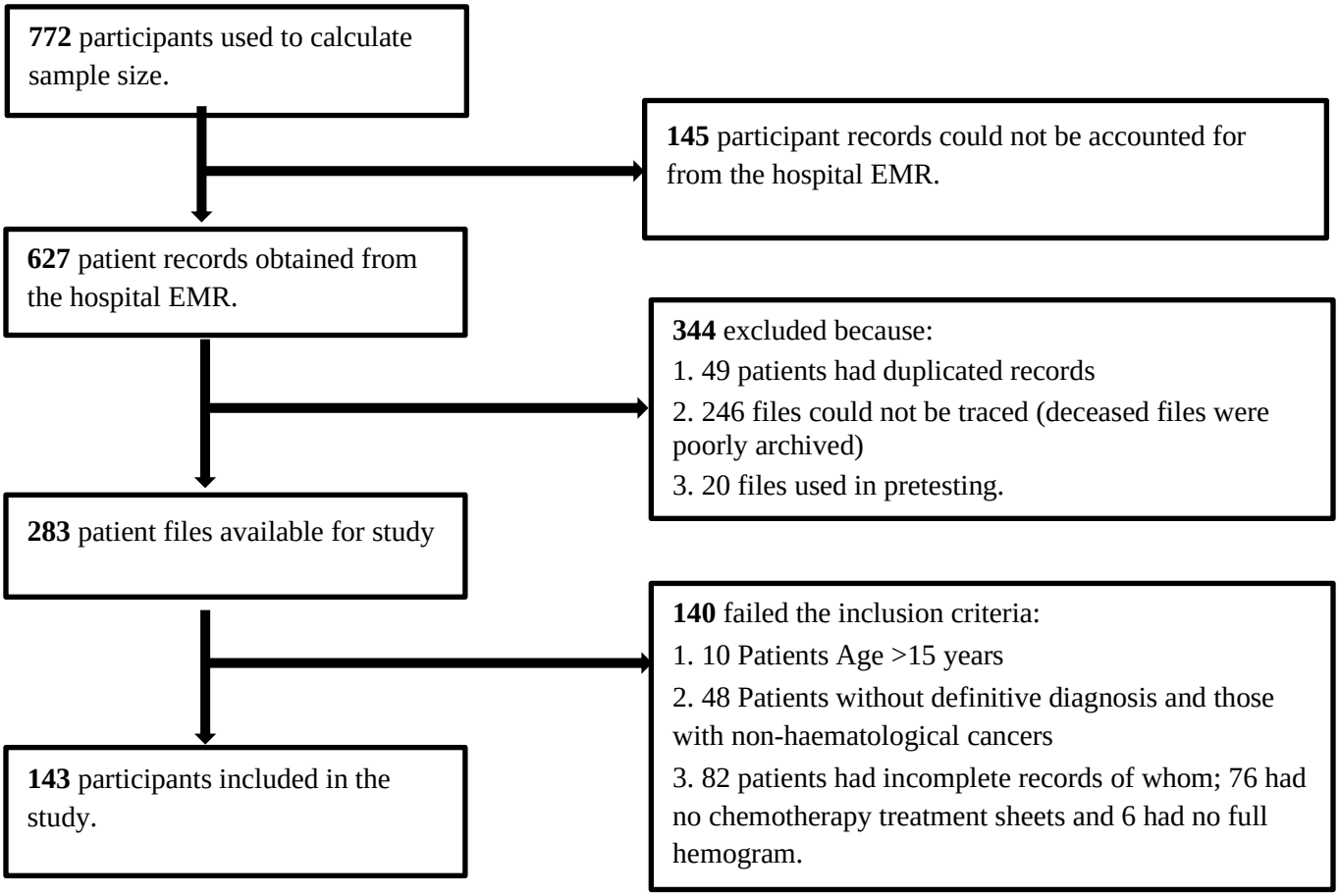

Figure 4. 1 Consort diagram for recruitment of participants

4.3 Descriptive analysis

4.3.1 Sociodemographic characteristics

The sociodemographic characteristics of 143 participants are shown in **Table 4.1**. There were 90 (62.9%) males and 53 (37.06%) females. The median age of the study participants was 7 [5, 11] years with youngest and oldest participants aged 1 and 15 years respectively. The median body surface area (BSA) was 0.84 (0.69, 1.09) m^2. The median Body Mass Index (BMI) was 15.15 [13.91, 16.80] kg/m^2. One hundred and eighteen (83.92%) participants were underweighting and only 3 (2.10%) were obese.

Table 4. 1 Sociodemographic characteristics

Variable	**Category**	**Frequency (%)**
Gender (n=143)	Male	90 (62.94)
	Female	53 (37.06)
Age (Years) (n=143)	<10 years	91 (63.64)
	≥ 10 years	52 (36.36)
BSA (m^2) (n=139)	<1	132(94.96)
	≥1	7(5.04)
BMI (kg/m^2) (n=139)	Underweight (<18.5)	121 (84.62)
	Normal Weight (18.5-24.9)	15 (10.49)
	Overweight (25-29.9)	1 (0.70)
	Obesity ≥ 30)	2 (1.40)

4.3.2 Clinical characteristics

The study included six haematological cancers managed at Kenyatta National Hospital where Acute Lymphoblastic Leukaemia was the most common (75,52.45%) as shown in **table 4.2, 4.3** and **4.4**. Majority of the ALL cases were morphologically classified as L2 at diagnosis. Most of the patients were managed with chemotherapy alone (141,98.6%) with majority of the regimens used having three or more agents (31,83.8%). A larger proportion of the patients included in the study were at induction phase (56,39.2%) of treatment.

Table 4. 2 Clinical characteristics (n=143)

Variable	Category	Frequency (n)	%
Type of cancer	Acute Lymphoblastic Leukaemia	75	52.45
	Chronic Lymphoblastic Leukaemia	3	2.10
	Acute Myeloid Leukaemia	13	9.09
	Chronic Myeloid Leukaemia	4	2.80
	Non-Hodgkin's Lymphoma	34	23.78
	Hodgkin's Lymphoma	14	9.79
Stage Cancer:	Stage 1	1	0.7
*Stage- HL, NHL	Stage 2	7	4.9
*Morphology-ALL, AML	Stage 3	4	2.8
	Stage 4	9	6.3
	L1	2	1.4
	L2	41	28.7
	L3	6	4.2
	M1	1	0.7
	M2	4	2.8
	M3	0	0.0
	M4	1	0.7
	Not Classified	67	46.9

Table 4. 3 Treatment modalities and number of agents per regimen

Variable	Category	Frequency (n)	%
Treatment Modalities (n=143)	Chemotherapy	141	98.6
	Chemotherapy + Radiotherapy	2	1.4
Number of Medications Per Regimen (n=37)	1	2	5.4
	2	4	10.8
	≥3	31	83.8

Table 4. 4 Treatment phase and comorbidities

Variable	Category	Frequency (n)	%
Treatment phase (n= 143)	Induction	56	39.2
	Consolidation	30	21.0
	Maintenance	37	25.9
	Cycle 1	5	3.5
	Cycle 2	2	1.4
	Cycle ≥3	3	2.1
	Not indicated	10	7.0
Number of comorbidities (n=143)	0	75	52.4
	1	31	21.7
	≥2	37	25.9

4.3.3 Baseline Laboratory Values

Absolute neutrophil count was low amongst 70 (48.9%) patients at diagnosis of the haematological cancers. Similar trend was observed with haemoglobin where 91(63.6%) patients were anaemic, **table 4.5**.

Table 4. 5 Baseline Laboratory values

Parameter	**Low n (%)**	**Normal n (%)**	**High n (%)**
WBC	43(30.1)	57(39.8)	43(30.1)
ANC	70(48.9)	60(42.0)	13(9.1)
Hb	91(63.6)	50(35.0)	2(1.4)
Platelets	53(37.1)	67(46.8)	23(16.1)
Albumin	1(1.3)	0(0.0)	75(98.7)
LDH	16(15.5)	42(40.8)	45(43.7)
ALT	-	59(77.6)	17(22.4)
AST	-	56(72.7)	21(27.3)
Serum Creatine	72(60.5)	45(37.8)	2(1.7)
BUN	117(97.5)	2(1.7)	1(0.8)

4.3.4 Types of chemotherapy regimens administered

Thirty-seven different types of chemotherapy regimens were used (**Table 4. 6**). The most common were 6-Mercaptopurine-Methotrexate-Vincristine-Adriamycin-Cyclophosphamide (26,18.2%) followed by Vincristine-Daunorubicin or Doxorubicin-Prednisolone-Methotrexate (14,9.8%) and Cyclophosphamide-Vincristine-Cytarabine (14,9.8%).

Table 4. 6 Regimen of chemotherapy administered (n=143)

Specific Regimen	Frequency	%
6-MP /Methotrexate/Vincristine/Adriamycin/Cyclophosphamide	26	18.2
Vincristine/Daunorubicin or Doxorubicin/Prednisolone/Methotrexate	14	9.8
Cyclophosphamide/Vincristine/Cytarabine	14	9.8
Cyclophosphamide/Doxorubicin/Vincristine/Prednisolone/Methotrexate (CHOP)	13	9.1
Cyclophosphamide/Vincristine/Procarbazine/Prednisolone/Hydroxydaunorubicine (CHOPP)	7	4.9
Prednisolone/Vincristine/Doxorubicin/L-Asparaginase/Methotrexate	7	4.9
Cyclophosphamide/Cytarabine/ 6-MP /Methotrexate	5	3.5
Doxorubicin/Bleomycin/Vinblastine/Dacarbazine (ABVD)	5	3.5
Adriamycin/cytarabine/etoposide	5	3.5
Ifosfamide/Etoposide/Carboplatin	4	2.8
Vincristine/Daunorubicin or Doxorubicin/Dexamethasone (VAP)	3	2.1
Vincristine/ Prednisolone/ 6-MP /Methotrexate	3	2.1
Hydroxyurea	3	2.1
Cytarabine/ Doxorubicin or daunorubicin	3	2.1
Others	23	21.7

4.4 Prevalence of chemotherapy induced neutropenia.

Neutropenia developed in majority (111, 77.6%) of participants after initiation of chemotherapy, **Figure 4.2**.

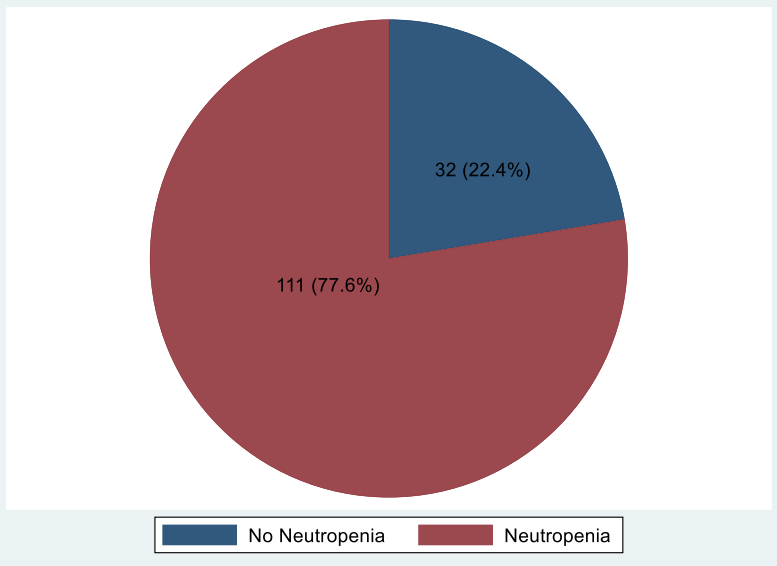

Figure 4. 2 Prevalence of chemotherapy induced neutropenia**.**

4.5: Predictors of neutropenia

Chi square test for independence was used to determine presence of significant association between neutropenia and the other parameters. The level of significance (α) was set at 0.05. logistic regression model was used to determine the association between neutropenia and the independent variables. Bivariate logistic regression was conducted for variables with p-value of less than 0.25 followed by Multivariate logistic regression.

4.5.1 Relationship between sociodemographic characteristics and neutropenia

There was no statistically significant relationship between sociodemographic characteristics and neutropenia as shown in **table 4. 7**.

Table 4. 7 Relationship between sociodemographic characteristics and neutropenia

Variable	Category	Neutropenia		P-value
		Yes	No	
Gender (n=143)	Male	11	42	0.721
	Female	21	69	
Age (Years) (n=143)	<10 years	16	75	0.069
	≥ 10 years	16	36	
BSA (m^2) (n=139)	<1	30	102	0.661*
	≥1	2	5	
BMI (kg/m^2) (n=143)	<18.5	26	95	0.265
	≥18.5	6	12	

Key: **Bolded**- *-Fishers Exact has been used

4.5.2 Relationship between clinical characteristics and neutropenia

Neutropenia was significantly associated with Acute Lymphoblastic Leukaemia, Chronic Lymphoblastic Leukaemia and Hodgkin's Lymphoma as shown in **table 4.8, 4.9 and 4.10**. Morphologically, L2 was significantly associated with neutropenia. The induction, consolidation, maintenance, and cycle two phases of treatment were significantly associated with neutropenia. Comorbidities such as hypertension, heart failure, and thrombocytopenia had statistically significant association with neutropenia.

Table 4. 8 Relationship between type and stage of cancer and neutropenia

Variable	Category		Neutropenia		p-value
		Y/N	No	Yes	
Type of cancer	ALL	No Yes	24 8	44 67	**0.001**
	CLL	No Yes	29 3	111 0	**0.010***
	AML	No Yes	30 2	100 11	0.733*
	CML	No Yes	30 2	100 11	0.216*
	NHL	No Yes	22 10	86 24	0.271
	HL	No Yes	25 7	104 7	**0.009**
Stage of Cancer *Stage- NHL, HL *Morphology -ALL, AML	Stage 1	No Yes	32 0	110 1	1.000*
	Stage 2	No Yes	29 3	107 4	0.187*
	Stage 3	No Yes	30 2	109 2	0.216*
	Stage 4	No Yes	31 1	103 8	0.684*
	L1	No Yes	32 0	109 2	1.000*
	L2	No Yes	28 4	72 37	**0.026***
	L3	No Yes	31 1	106 5	1.000*
	M1	No Yes	32 0	110 1	1.000*
	M2	No Yes	31 1	108 3	1.000*
	M4	No Yes	32 0	110 1	1.000*

Key: **Bolded**- statistically significant, *- Fisher's Exact has been used

Table 4. 9 Relationship between treatment modalities and phase and neutropenia

Variable	Category		Neutropenia		p-value
		Y/N	No	Yes	
Treatment Modalities	Chemotherapy	No Yes	0 32	2 109	1.000*
	Chemo+ RT	No Yes	32 0	109 2	1.000*
Treatment Phase	Induction	No Yes	27 5	60 51	**0.002**
	Consolidation	No Yes	31 1	82 29	**0.003***
	Maintenance	No Yes	16 16	90 21	**0.001**
	Cycle 1	No Yes	30 2	108 3	0.311*
	Cycle 2	No Yes	30 2	111 0	**0.049***
	Cycle ≥3	No Yes	31 1	109 2	0.535*

Key: **Bolded**- Statistically significant, *- Fisher's Exact has been used

Table 4. 10 Relationship between comorbidities and type of cancer

Variable	Category		Neutropenia		p-value
		Y/N	No	Yes	
Comorbidities	Hypertension	No Yes	30 2	11 0	**0.049***
	Liver Disease	No Yes	30 2	107 4	0.616*
	Renal Disease	No Yes	31 1	110 1	0.399*
	Heart Failure	No Yes	29 3	110 1	**0.035***
	Anaemia	No Yes	22 10	65 45	0.324
	Thrombocytopenia	No Yes	28 4	72 39	**0.016***

Key: **Bolded**- Statistically significant, *- Fisher's Exact has been used

4.5.3 Relationship between chemotherapy regimens and neutropenia

Neutropenia was significantly associated with combinations of Cyclophosphamide/ Vincristine/ Cytarabine, 6-MP/ Methotrexate/ Vincristine/ Adriamycin/ Cyclophosphamide as well as the single agent hydroxyurea as shown in **table 4.11** and **appendix 6**.

Table 4. 11 Relationship between chemotherapy regimens used and neutropenia (n=143)

Regimen	Category	Neutropenia		p-value
		No	Yes	
Cyclophosphamide/Vincristine/Cytarabine	No Yes	32 0	97 14	**0.040***
6-MP/ Methotrexate/Vincristine/ Adriamycin/Cyclophosphamide	No Yes	20 12	97 14	**0.001**
Cyclophosphamide/Vincristine/ Procarbazine/ Prednisolone/Hydroxydaunorubicin (CHOPP)	No Yes	29 3	107 4	0.187*
Vinblastine/6-MP	No Yes	31 1	111 0	0.224*
Hydroxyurea/ Cytarabine	No Yes	31 1	111 0	0.224*
Hydroxyurea	No Yes	29 3	111 0	**0.010***
Hydroxyurea/ Imatinib	No Yes	31 1	111 0	0.224*

Key: **Bolded**- statistically significant, *- Fisher's Exact has been used

4.5.4 The Overall predictors of neutropenia

In the bivariate analysis, advanced age, ALL, HL, L2 morphological classification of ALL, induction phase, consolidation and maintenance phases, heart failure, thrombocytopenia, and use of the 6-Mercaptopurine/ Methotrexate/Vincristine/Adriamycin/Cyclophosphamide regimen were significantly associated with neutropenia as shown in **table 4.12**. However, in the multivariate analysis, only induction and consolidation phases of treatment of haematological cancers were significantly associated with neutropenia.

Patients in the induction phase of treatment were 9.195 times more likely to develop neutropenia compared to patients who were in other phases of treatment: AOR 9.195(95% CI: 2.046-41.318; p=0.004). Similarly, patients in the consolidation phase of management had higher odds (10.593)

of developing neutropenia than patients who were not on consolidation phase of treatment: AOR 10.593 (95% CI: 0.97-115.651; p=0.053).

Table 4. 12 Bivariate and multivariate logistic regression for predictors of neutropenia

Independent variable	**Bivariate analysis**		**Multivariate analysis**	
	COR (95% CI)	**p-value**	**AOR (95% CI)**	**p-value**
Age (<10 years, ≥10 years)	0.48(0.216-1.066)	0.072	0.506(0.176-1.451)	0.205
ALL (absent, present)	4.568(1.188-11.079)	**0.001**	1.705(0.406-7.165)	0.466
CML (absent, present)	0.275(0.037-2.036)	0.206	0.911(0.058-14.293)	0.947
HL (absent, present)	0.24(0.077-0.748)	**0.014**	0.227(0.029-1.777)	0.158
Stage 2 (absent, present)	0.361(0.077-1.706)	**0.199**	2.152(0.156-29.638)	0.567
Stage 3 (absent, present)	0.275(0.037-2.036)	**0.206**	0.719(0.055-9.475)	0.802
L2 (absent, present)	3.597(1.174-11.027)	**0.025**	2.509(0.513-12.264)	0.256
Induction (absent, present)	4.59(1.647-12.788)	**0.004**	9.195(2.046-41.318)	**0.004**
Consolidation (absent, present)	10.963(1.431-83.965)	**0.021**	10.593(0.97-115.651)	0.053
Maintenance (absent, present)	0.233(0.101-0.541)	**0.001**	1.699(0.277-10.423)	0.567
Heart failure (absent, present)	0.088(0.009-0.876)	**0.038**	0.175(0.012-2.591)	0.205
Thrombocytopenia (absent, present)	3.791(1.24-11.595)	**0.019**	1.708(0.406-7.178)	0.465
R3 (absent, present)	0.241(0.969-0.597)	**0.002**	0.286(0.054-1.489)	0.137
R10 (absent, present)	0.361(0.077-1.706)	0.199	0.658(0.176-1.451)	0.720

Key: AOR: adjusted odds ratio, COR: Crude Odds Ratio,: R3: 6-MP/ Methotrexate/ Vincristine/ Adriamycin/ Cyclophosphamide, R10: Cyclophosphamide/ Vincristine/ Procarbazine/ Prednisolone/ Hydroxydaunorubicin (CHOPP), **Bolded**: statistical significance (p<0.05).

4.6 Management of Neutropenia

4.6.1 Prevalence of febrile neutropenia and neutropenia resolution time

Febrile neutropenia developed in 17(15.6%) patients who had at least one record of temperature in the patient files. It took more than seven days for neutropenia to resolve in majority (71, 63.39%) .of the patients,

4.6.2 Management strategies of febrile neutropenia

Most of the patients with febrile neutropenia were managed with GCSF (21, 18.8%) followed by combination of antibacterial and granulocyte colony stimulating factor, at 18 (16.1%), **table 4.13**. The only treatment interruption reported was treatment delay accounting for 15 (13.5%). Amoxicillin clavulanic acid was the most commonly used antibiotic in the management of neutropenia, 17 (15.32%) while fluconazole was the most commonly used antifungal, 10 (9.0%) as shown in **table 4.14**. Nystatin mouth wash was the most preferred mouthwash even when used without antifungal, 10(9.0%).

Table 4. 13 Management strategies of febrile neutropenia

Management strategy	**Category**	**Frequency (%)**
Anti-infectives± GCSF (n=111)	GCSF	21(18.9)
	Antibacterial+GCSF	18(16.2)
	Antibacterial	15(13.5)
	Antibacterial+ antifungal	12(10.8)
	Antibacterial+ antifungal+GCSF	10(9.0)
	Antifungal +GCSF	4(3.6)
	Antibacterial + Antifungal +Antiprotozoal + GCSF	4(3.6)
	Antibacterial + Antifungal + Antiviral	3(2.7)
	Antiviral +GCSF	2 (1.8)
	Antibacterial + Antiprotozoal	1 (0.9)
	Antibacterial +Antiviral +GCSF	1(0.9)
	Antibacterial + Antiviral	1 (0.9)
	Antibacterial+ Antifungal+ Antiviral +GCSF	1 (0.9)
	Antifungal	1 (0.9)
	Antiprotozoal	1 (0.9)
	Antiviral	1 (0.9)
	Antibacterial + Antifungal + Antiprotozoal	1 (0.9)
Treatment interruption (n=111)	Treatment delay	15(13.5%)

Table 4. 14 Specific anti-infectives used in management of neutropenia

Anti-infective	Category	Frequency (%)
Antibacterials (n=111)	Amoxicillin/clavulanic acid	17(15.3)
	Ceftriaxone	8 (7.2)
	Sulfamethoxazole/Trimethoprim	5 (5.5)
	Meropenem	4 (3.7)
	Ceftriaxone+ Amoxicillin/Clavulanic Acid	3 (2.7)
	Ceftriaxone + Cefuroxime	2 (1.8)
	Ceftriaxone + Flucloxacillin + Azithromycin	2 (1.8)
	Cefuroxime+ Amoxicillin/Clavulanic acid	2 (1.8)
	Ceftriaxone + Metronidazole	2 (1.8)
	Sulfamethoxazole/Trimethoprim + Ciprofloxacin	2 (1.8)
	Flucloxacillin	2 (1.8)
	Ceftazidime + Amikacin	2 (1.8)
	Benzylpenicillin+ Gentamycin	1 (0.9)
	Ceftriaxone + Amoxicillin/Clavulanic Acid + Flucloxacillin	1 (0.9)
	Ceftazidime + Amikacin + Metronidazole	1 (0.9)
	Levofloxacin	1 (0.9)
	Ceftriaxone + Flucloxacillin	1 (0.9)
	Ceftriaxone + Ceftazidime + Meropenem + Flucloxacillin	1 (0.9)
	Ciprofloxacin	1 (0.9)
	Amoxicillin/Clavulanic Acid + Sulfamethoxazole/Trimethoprim	1 (0.9)
	Cefuroxime	1 (0.9)
	Metronidazole	1 (0.9)
	Ceftriaxone + Azithromycin	1 (0.9)
	Piperacillin/Tazobactam + Sulfamethoxazole/Trimethoprim	1 (0.9)

Anti-infective	Category	Frequency (%)
	Piperacillin/Tazobactam	1 (0.9)
	Piperacillin/Tazobactam + Ceftriaxone	1 (0.9)
	Piperacillin/Tazobactam + Cefuroxime	1 (0.9)
	Ceftazidime + Cefuroxime + Amoxicillin/Clavulanic Acid	1 (0.9)
	Ceftazidime + Amoxicillin/Clavulanic Acid	1 (0.9)
	Sulfamethoxazole/Trimethoprim + Vancomycin	1 (0.9)
	Ceftriaxone + Amikacin + Amoxicillin/Clavulanic Acid	1 (0.9)
	Flucloxacillin + Metronidazole + Amikacin	1 (0.9)
	Flucloxacillin + Amoxicillin/Clavulanic Acid	1 (0.9)
	Vancomycin + Metronidazole + Flucloxacillin + Meropenem	1 (0.9)
Antifungals and Mouthwashes (n=111)	Nystatin	10 (9.0)
	Fluconazole	10 (9.0)
	Fluconazole + Nystatin	7 (6.31)
	Chlorhexidine Mouthwash	3 (2.7)
	Fluconazole + Chlorhexidine Mouthwash	1 (0.9)
	Chlorhexidine + Nystatin	1 (0.9)
	Metronidazole	1 (0.9)
Antivirals (n=111)	Acyclovir	9 (8.11)
Antiprotozoals (n=111)	Artesunate	4 (3.6)
	Artemether Lumefantrine	2 (1.8)
	Artemether Lumefantrine + Artesunate	1 (0.9)

CHAPTER 5: DISCUSSION, CONCLUSSION AND RECOMMENDATIONS

5.1 Introduction

This chapter explores the research findings, providing conclusions and recommendations drawn from the results of the study

5.2 Discussion

In this study, most of the patients were below 10 years. This group accounts for most of the paediatric blood cancers which concurs with a study done at a tertiary hospital in Kenya (59) . Unlike in other studies where advanced age (Above 65 years) has positively been associated with neutropenia, (23,37,40,60–66), such a relationship was not observed. This is probably because the study was done in paediatrics whose bone barrow is highly active unlike in the elderly where there is immunosenescence (67). Additionally, the paediatric population rarely present with comorbidities making them less susceptible to chemotherapy induced neutropenia compared to the elderly.

Male predominance was observed which is in line with existing literature (68). Male gender has also been linked with high cases of ALL ranging from 57-65% of all the paediatric ALL cases (47,69–72). In concordance with other studies on solid tumors, there was no significant association between gender and neutropenia (23). However, these findings contrast a study that reported that at baseline, males are more predisposed to neutropenia than females (73).

Both BSA and BMI had no association with neutropenia consistent with a previous study done on breast cancer (23). In addition, previous studies by Schwenkglenks et al, Moreau et al and Lakey et al linked BSA above $2m^2$ with neutropenia (38,42,61). The contrasting finding in our study might be because our study participants were paediatrics with BSA below $2m^2$.

Acute Lymphoblastic Leukaemia was the most common paediatric haematological cancer accounting for 52.45% of the cancer cases. This resonates with a previous study done by Mutua et al (59). Similarly, a report on Epidemiology of Childhood Cancer reported that leukaemias are the most common paediatric cancers and ALL accounts for about three-fourths of the leukaemias (74,75). ALL, CLL and HL were significantly associated with neutropenia Most of the ALL participants had L2 morphological classification.

Chemotherapy was the main modality used in management of paediatric haematological cancers at 98.6%. This reflects the ideal settings since radiation therapy in blood cancers is only limited to oncological emergencies such as bone pain, nodal involvement common in lymphomas, as well as CNS and testicular involvement. Combination therapy is usually preferred in management of blood cancers and offer synergistic effect. This explains why 83.8% of the regimens used in the study contained at least three agents. Treatment modalities were not significantly associated with neutropenia.

There were few comorbidities observed among the participants with only 25.9% of the participants presenting with two or more comorbidities. Hypertension, heart failure, and thrombocytopenia were statistically related with neutropenia. Cardiovascular diseases such as heart diseases and hypertension have previously been associated with neutropenia (49,65,66). This is probably because the cardiovascular diseases contribute to hypoxia which impairs neutrophil function via impaired release of oxygen radicals (76). Studies by Chao et al and Bailey et al also reported association between thrombocytopenia and neutropenia (51,77). Based on available evidence, it is plausible to note that both thrombocytopenia and neutropenia are mediated through bone marrow suppression.

Majority of the participants were either in induction or consolidation, phases of treatment. The induction, consolidation, maintenance, and cycle 2 phases of treatment were significantly associated with neutropenia at bivariate logistic regression. However, multivariate analysis results confirmed that being in the induction or consolidation phases of treatment were the only independent predictors of neutropenia. A similar relationship was found in studies done in Memphis, USA, and Colombia that linked these phases with increased infections related to neutropenia (78,79). This is probably related to myelosuppressive haematological cancers especially ALL which presents with pancytopenia. In addition, the intensive multi-agent chemotherapy used in these phases of treatment can cause profound long-lasting neutropenia.

The most common regimen used in management of the haematological cancers contained 6-mercaptopurine, methotrexate, vincristine, doxorubicin, and cyclophosphamide which according to the protocol that was highly used in the facility during the study period was the preferred regimen for maintenance therapy in ALL (80). This is supported by the fact that majority of the cases in the study were ALL. Based on the findings of this study, the most common regimen was

expected to cover patients in either the induction or consolidation phases. However, this was not the case, and the findings could be supported by the fact that different protocols are used in induction and consolidation phases depending on whether the patient is on initial or repeat of these phases.

Combination of cyclophosphamide/ vincristine/ cytarabine, 6-mercaptopurine/ methotrexate/ vincristine/ doxorubicin/ cyclophosphamide and the single agent hydroxyurea were associated with neutropenia. Various regimens and single agents have been associated with neutropenia in several studies. For instance, studies by Okunaka et al and Njuguna et al reported that alkylating agents, antimetabolites, tumor antibiotics, platinums and plant derived antibiotics are associated with infectious neutropenia (28,64). Shayne et al found out that regimens containing cyclophosphamide, etoposide or ifosfamide increases the risk of neutropenia (81). Yasunori et al equally found out that platinum and taxanes containing regimens were also associated with chemotherapy induced neutropenia (82). It is paramount to note that all these studies were done in the adult population and children are known to tolerate anticancer agents better if well dosed hence supporting the findings of this study. This ease of tolerability is probably because of the high cell turnover in children.

The prevalence of neutropenia after initiation of chemotherapy was high similar to findings of more than 80% among the haematological cancers reported in a Belgium study (46). This is higher than what was observed in gynaecologic malignancies in Japan and USA (61,82) Neutropenic fever developed in 15.6% of the patients, higher than is observed in gynaecologic, epithelial ovarian cancer, breast and other solid tumors (82–85). This is probably because the high number of patients with haematological malignancies developing neutropenia will progress to develop febrile neutropenia. It took more than seven days for most patients with neutropenia to recover. This observation was in concordance with a study on haematological malignancies by Kuntegowdanahalli et al (86).

Most of the participants received granulocyte colony stimulating factors (GCSF) either singly or in combination with other agents for the management of febrile neutropenia. This was slightly lower than the 35% reported by Ditte et al on AML (87). The difference could be because majority of the patients in our study had ALL and were in the induction phase, where the use of GCSF is controversial. NCCN guidelines recommends use of GCSF when there is intermediate to high risk

of neutropenia while ESMO guidelines recommends use when risk is ≥20% (56,88). We could not adequately establish whether the indication for GCSF was based on ESMO or NCCN guidelines since none of the patient records had documented risk stratification.

The most preferred antibiotics for the management of neutropenia were amoxicillin clavulanic acid and ceftriaxone used alone or with other agents. The preference was consistent with the recommendation by the local treatment guidelines for patients at both low risk and high risk of developing neutropenia (24). For the low risk, the Kenya Cancer Treatment Protocols recommends oral ciprofloxacin or amoxicillin + clavulanic acid while for the high risk, it recommends monotherapy of cefepime, ceftazidime, ceftriaxone or meropenem or a combination of aminoglycoside/ antipseudomonal or penicillin/beta-lactamase inhibitor (24). In the advent of antimicrobial resistance, combinations of amoxicillin-clavulanic acid and ciprofloxacin are most preferred necessitating the need for review of the Kenyan guidelines (88).

We observed that treatment delay was common among the neutropenic patients. Previous studies on breast cancer by Ruth et al and diffuse large B cell lymphoma (DLBCL) by Bailey et al found out that febrile neutropenia was significantly associated with dose delays (77,85).

5.3 Conclusion

There was high prevalence of neutropenia among the participants. Induction and consolidation phases of treatment were found to be significantly associated with chemotherapy induced neutropenia. The use of GCSF, combination of antibiotics or chemotherapy deferment were used in the management of febrile neutropenia.

5.4 Limitations of the Study

The study was carried out in a small study population within one hospital making it hard to generalize the findings. The retrospective design and overreliance on pre-recorded information in the participants file limited information such as treatment interruption that could not be adequately verified as presented in the patient treatment sheets. For instance, treatment delay could be interpreted as supply chain inadequacy and not necessarily due to neutropenia. In addition, many files were missing from the filling area limiting the sample size. This study did not explore all factors associated with neutropenia such as use of other immunosuppressive drugs, and malnutrition whose data could not be obtained from the files.

5.5 Recommendations

5.5.1 Recommendations for policy and practice

1. The facility should ensure all records are properly stored as recommended to inform future research. Patients within this study were mainly alive and this was largely because of the poor storage of deceased patients' records at Kenyatta National Hospital.

2. The hospital and by extension, the Ministry of Health should develop clinical practice guidelines for the use of antibiotics among neutropenic patients and ensure that they are regularly updated. Improper selection of antibiotics and inappropriate combinations of antibacterials for prophylaxis and management of neutropenia was noted.

5.5.2 Recommendations for further research

Prospective research in representative populations should be carried out to find out the determinants of neutropenia among paediatric haematological cancer patients. Temporal sequence would easily be detected with this study and data gaps together with the sample size issues experienced in this study would easily be addressed. Identification of these factors will permit flagging off patients at greatest risk for adequate prophylactic measures.

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APPENDICES

APPENDIX 1: ELIGIBILITY FORM

1. Subject name/ ID……

2. **Inclusion/ Exclusion Criteria**

Criteria	**Yes**	**No**
a) Inclusion criteria		
i. Age of 15 years and below with confirmed haematological cancer.	☐	☐
i. Received chemotherapy at KNH.	☐	☐
b) Exclusion criteria		
i. Any history of allogenic stem cell transplantation within the previous year they have.	☐	☐
ii. Have incomplete records	☐	☐

3. **Statement of eligibility**

The subject is **ELIGIBLE**……. ☐ / **NOT ELIGIBLE**…… ☐ to participate in the study.

If the subject is excluded from the study, the reason for exclusion **…….....**

.....……

APPENDIX 2: DATA ABSTRACTION FORM

Study title: Predictors and management of febrile neutropenia among paediatric patients with haematological malignancies at Kenyatta National Hospital.

Study number……. Date of data collection……..

Date of admission……...

Section A: Patient characteristics

1. Gender Male [ ] Female [ ]
2. Age (in years) ……
3. Height (in centimetres) …….
4. Weight (in Kg) …….....
5. BSA (in square meters) …….

SECTION B: CLINICAL PREDICTORS OF CHEMOTHERAPY INDUCED NEUTROPENIA

1. Type of haematological malignancies
    a. Acute Lymphoblastic Leukaemia [ ]
    b. Chronic Lymphoblastic Leukaemia [ ]
    c. Acute Myeloid Leukaemia [ ]
    d. Chronic Myeloid Leukaemia [ ]
    e. Non-Hodgkin's Lymphoma [ ]
    f. Hodgkin's Lymphoma [ ]
2. Cancer stage:
    a. Stage I [ ]
    b. Stage II [ ]
    c. Stage III [ ]
    d. Stage IV [ ]

e. Not classified [ ]

3. Treatment modalities
    a. Chemotherapy [ ]
    b. Chemotherapy + Radiotherapy [ ]

4. Chemotherapy regimen used…….
5. Treatment phase (for AML, CML, ALL, CLL or NHL) /cycle (for HL)
    a. Induction [ ]
    b. Consolidation [ ]
    c. Maintenance [ ]
    d. Cycle 1 [ ]
    e. Cycle 2 [ ]
    f. Cycle 3 and above [ ]

6. Treatment intent
    a. Curative [ ]
    b. Palliative [ ]

7. Comorbidities (Tick all that apply)
    a. Hypertension [ ]
    b. Diabetes [ ]
    c. Liver Disease [ ]
    d. Renal disease [ ]
    e. Heart failure [ ]
    f. COPD/ Asthma [ ]
8. Baseline laboratory values
    a. WBC (10^3 cells/mm^3) ……
    b. ANC (*10^9/ml) ……
    c. Hb (g/dl) …….
    d. Platelet (10^3/mm^3) …….

e. Albumin (g/dl) ……....
f. LDH (U/l) ……...
g. Serum Creatine (mg/dl) …….
h. ALT (U/l) ……
i. AST (U/l) …….
j. BUN (mg/dl) ……

SECTION C: MANAGEMENT OF CHEMOTHERAPY INDUCED NEUTROPENIA

1. Time since the last dose of chemotherapy (before diagnosis of CIN in days) …….
2. Neutrophil count at diagnosis of CIN (*10^9/ml) ……
3. Temperature at time of CIN diagnosis (^{o}c)…….....
4. Neutropenia resolution time (in days)
   a. ≤ 7 [ ]
   b. >7 [ ]

5. Prophylactic use of (Tick all that apply)
   a. Antibiotics [ ]
   b. G-CSF [ ]
6. Treatment using (Tick all that apply)
   a. Antibacterial [ ]
   b. Antifungals [ ]
   c. Antivirals [ ]
   d. Antiprotozoals [ ]
   e. G-CSF [ ]
7. Treatment interruption (Tick all that apply)
   a. Dose reduction [ ]
   b. Treatment delay [ ]
   c. Change of regimen [ ]

SECTION D: PREVALENCE OF NEUTROPENIA

Developed at least one episode of neutropenia within the study period: Yes [ ], No [ ]

APPENDIX 3: REFERENCE RANGES

Parameter	Reference Range
WBC (10^3 cells/mm3)	4-10
ANC (*10^9/ml)	2-7.8
Hb (g/dl)	12-16
Platelet (10^3/mm3)	144-440
Albumin (g/dl)	3.8-4.6
LDH (U/l)	225-480
Serum Creatine (micromoles/l)	65.4-119.3
ALT (U/l)	≤40
AST (U/l)	≤40

APPENDIX 4: FORMULAS

1. BSA= $\sqrt{\frac{Height\ (cm) * Weight\ (kg)}{3600}}$

2. BMI= $\frac{Weight\ (kg)}{height^2\ \ (in\ meters)}$

APPENDIX 5: NUMBER OF PATIENTS RECEIVING EACH SPECIFIC REGIMEN

CODE	REGIMEN	Frequency	%
R1	Vincristine/Daunorubicin or Doxorubicin/Prednisolone/Methotrexate	14	9.8
R2	Cyclophosphamide/Vincristine/Cytarabine	14	9.8
R3	6-MP /Methotrexate/Vincristine/Adriamycin/Cyclophosphamide	26	18.2
R4	Vincristine/Daunorubicin or Doxorubicin/Dexamethasone (VAP)	3	2.1
R5	Prednisolone/Vincristine/Daunorubicin/L-Asparaginase	0	0.0
R6	6-MP/Methotrexate	0	0.0
R7	Cytosine Arabinoside/Daunorubicin or doxorubicin/6-Thioguanine or 6-Mercaptopurine	2	1.4
R8	Doxorubicin or Daunorubicin/Cytarabine/6-Thioguanine or 6-Mercaptopurine	0	0.0
R9	Hydroxyurea/Busulphan/6-MP /Cytosine	0	0.0
R10	Cyclophosphamide/Vincristine/Procarbazine/Prednisolone/Hydroxydaunorubicin (CHOPP)	7	4.9
R11	Vinblastine/Chlorambucil/Prednisolone/Procarbazine/Doxorubicin (ChIPP)	0	0.0
R12	Cyclophosphamide/Vincristine/Procarbazine/Prednisone/Adriamycin/ Bleomycin/Vinblastine/Darcabazine (C/OPP/ABVD-salvage therapy)	0	0.0
R13	Cyclophosphamide/Doxorubicin/Vincristine/Prednisolone/Methotrexate (CHOP)	13	9.1
R14	Cyclophosphamide/Adriamycin/Cytarabine	1	0.7
R15	6-MPU /Methotrexate/Vincristine/Doxorubicin/Cytarabine	0	0.0
R16	Cyclophosphamide/Doxorubicin/Vincristine/Prednisolone/Bleomycin/ Methotrexate (CHOP-BLEO)	0	0.0
R17	6-MP /Vincristine	0	0.0
R18	Prednisolone/ Vincristine/Daunorubicin/ L-Asparaginase/Cytarabine/Methotrexate	2	1.4
R19	Cyclophosphamide/Cytarabine/ 6-MP /Methotrexate	5	3.5
R20	Vincristine/ Prednisolone/ 6-MP /Methotrexate	3	2.1

CODE	REGIMEN	Frequency	%
R21	Dexamethasone/Vincristine/Daunorubicin/L-Asparaginase/Methotrexate	2	1.4
R22	Cyclophosphamide/Cytarabine/6-MP /Methotrexate	1	0.7
R23	Prednisolone/Vincristine/L-Asparaginase/Methotrexate	2	1.4
R24	Vincristine/6-MP /Methotrexate	1	0.7
R25	Prednisolone/Vincristine/Doxorubicin/L-Asparaginase/Methotrexate	7	4.9
R26	Etoposide/L-Asparaginase/Methotrexate/Folinic Acid/Cytarabine	2	1.4
R27	Doxorubicin/Bleomycin/Vinblastine/Dacarbazine (ABVD)	5	3.5
R28	Cyclophosphamide/Vincristine/Prednisolone/Doxorubicin (COPAD	1	0.7
R29	Cyclophosphamide/Vincristine/Prednisolone/Methotrexate/Hydrocortisone (COP)	0	0.0
R30	Vincristine/Prednisolone/Methotrexate/Cyclophospamide/Doxorubicin /Hydrocortisone (COPADM1)	0	0.0
R31	Vincristine/Prednisolone/Methotrexate/Cyclophospamide/Doxorubicin /Cytarabine/Hydrocortisone (COPADM2)	1	0.7
R32	Methotrexate/Cytarabine/Hydrocortisone	2	1.4
R33	Cytarabine/Etoposide	0	0.0
R34	Vincristine/Prednisolone/Methotrexate/Cyclophosphamide/Doxorubicin	0	0.0
R35	Vincristine/Prednisolone/Cyclophosphamide/Doxorubicin	0	0.0
R36	Methotrexate/Cytarabine/Doxorubicin/Vincristine	1	0.7
R37	Cyclophosphamide/Vincristine/Doxorubicin/Methotrexate/Cytarabine/ Dexamethasone (HYPERCAVD)	2	1.4
R38	Cyclophosphamide/Vincristine/Prednisolone/Cytarabine/Methotrexate/ 6-MP	2	1.4
R39	Vinblastine/6-MP	1	0.7
R40	Ifosfamide/Etoposide/Carboplatin	4	2.8
R41	Adriamycin/cytarabine/etoposide	5	3.5
R42	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone-R-CHOP	1	0.7
R43	Hydroxyurea/ Cytarabine	1	0.7
R44	Hydroxyurea	3	2.1

CODE	REGIMEN	Frequency	%
R45	Hydroxyurea/ Imatinib	1	0.7
R46	Cytarabine/ Doxorubicin or daunorubicin	3	2.1
R47	Doxorubicin/ Bleomycin/ Vincristine/ Etoposide/ Cyclophosphamide/ Prednisolone (ABVEPC0	1	0.7
R48	Cytarabine/ Daunorubicin/ 6-MP	1	0.7
R49	Cyclophosphamide/ Doxorubicin/ Cytarabine/ Methotrexate	1	0.7
R50	Cytarabine	1	0.7
R51	Etoposide/Cytarabine/Doxorubicin	1	0.7
	TOTAL	143	100.0

APPENDIX 6: RELATIONSHIP BETWEEN CHEMOTHERAPY REGIMENS USED IN MANAGEMENT OF PAEDIATRIC HAEMATOLOGICAL CANCERS AND NEUTROPENIA

Code	Regimen	Category	Neutropenia		p-value
			No	Yes	
R1	Vincristine/Daunorubicin or Doxorubicin/ Prednisolone/ Methotrexate	No Yes	30 2	99 12	0.736
R2	Cyclophosphamide/Vincristine/Cytarabine	No Yes	32 0	97 14	**0.040***
R3	6-MP/ Methotrexate/ Vincristine/ Adriamycin/ Cyclophosphamide	No Yes	20 12	97 14	**0.001***
R4	Vincristine/ Daunorubicin or Doxorubicin/ Dexamethasone (VAP)	No Yes	32 0	108 3	1.000
R7	Cytosine Arabinoside/ Daunorubicin or doxorubicin/ 6-Thioguanine or 6-MP	No Yes	31 1	110 1	0.399
R10	Cyclophosphamide/ Vincristine/ Procarbazine/ Prednisolone/ Hydroxydaunorubicin (CHOPP)	No Yes	29 3	107 4	0.187
R13	Cyclophosphamide/Doxorubicin/ Vincristine/Prednisolone/Methotrexate (CHOP)	No Yes	31 1	99 12	0.298
R14	Cyclophosphamide/ Adriamycin/ Cytarabine	No Yes	32 0	110 1	1.000
R18	Prednisolone/ Vincristine/Daunorubicin/ L-Asparaginase/Cytarabine/Methotrexate	No Yes	32 0	109 2	1.000
R19	Cyclophosphamide/Cytarabine/ 6-MP / Methotrexate	No Yes	32 0	106 5	0.587
R20	Vincristine/ Prednisolone/ 6-MP / Methotrexate	No Yes	32 0	108 3	1.000
R21	Dexamethasone/Vincristine/Daunorubicin/ L-Asparaginase/Methotrexate	No Yes	32 0	109 2	1.000
R22	Cyclophosphamide/Cytarabine/6-MP / Methotrexate	No Yes	32 0	110 1	1.000
R23	Prednisolone/Vincristine/L-Asparaginase/ Methotrexate	No Yes	32 0	109 2	1.000
R24	Vincristine/6-MP /Methotrexate	No	32	110	1.000

Code	Regimen	Category	Neutropenia		p-value
			No	Yes	
		Yes	0	1	
R25	Prednisolone/Vincristine/Doxorubicin/ L-Asparaginase/Methotrexate	No Yes	32 0	110 1	1.000
R26	Etoposide/L-Asparaginase/Methotrexate/ Folinic Acid/Cytarabine	No Yes	32 0	109 2	1.000
R27	Doxorubicin/Bleomycin/Vinblastine/ Dacarbazine (ABVD)	No Yes	32 0	108 3	0.311
R28	Cyclophosphamide/Vincristine/Prednisolone/ Doxorubicin (COPAD	No Yes	32 0	110 1	1.000
R31	Vincristine/ Prednisolone/ Methotrexate/ Cyclophosphamide/ Doxorubicin/ Cytarabine/ Hydrocortisone (COPADM2)	No Yes	32 0	110 1	1.000
R32	Methotrexate/Cytarabine/Hydrocortisone	No Yes	31 1	110 1	0.399
R36	Methotrexate/ Cytarabine/ Doxorubicin/ Vincristine	No Yes	32 0	110 1	0.399
R37	Cyclophosphamide/ Vincristine/ Doxorubicin/ Methotrexate/ Cytarabine/ Dexamethasone (HYPERCAVD)	No Yes	32 0	109 2	1.000
R38	Cyclophosphamide/ Vincristine/ Prednisolone/ Cytarabine/ Methotrexate/6-MP	No Yes	31 1	110 1	0.399
R39	Vinblastine/6-MP	No Yes	31 1	111 0	0.224
R40	Ifosfamide/ Etoposide/ Carboplatin	No Yes	31 1	108 3	1.000
R41	Adriamycin/ cytarabine/ etoposide	No Yes	31 1	107 4	1.000
R42	Rituximab/ cyclophosphamide/ doxorubicin/ vincristine/ prednisolone- R-CHOP	No Yes	32 0	110 1	1.000
R43	Hydroxyurea/ Cytarabine	No Yes	31 1	111 0	0.224

Code	Regimen	Category	Neutropenia		p-value
			No	Yes	
R44	Hydroxyurea	No Yes	29 3	111 0	**0.010***
R45	Hydroxyurea/ Imatinib	No Yes	31 1	111 0	0.224
R46	Cytarabine/ Doxorubicin or daunorubicin	No Yes	32 0	108 3	1.000
R47	Doxorubicin/Bleomycin/Vincristine/ Etoposide/ Cyclophosphamide/ Prednisolone (ABVEPC0	No Yes	32 0	110 1	1.000
R48	Cytarabine/ Daunorubicin/ 6-MP	No Yes	32 0	110 1	1.000
R49	Cyclophosphamide/ Doxorubicin/ Cytarabine/ Methotrexate	No Yes	32 0	110 1	1.000
R50	Cytarabine	No Yes	32 0	110 1	1.000
R51	Etoposide/Cytarabine/Doxorubicin	No Yes	32 0	110 1	1.000

APPENDIX 7: KNH-UON ERC APPROVAL

UNIVERSITY OF NAIROBI
FACULTY OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/526

20th December, 2022

APPROVED
20 DEC 2022

Patrick Muthini John
Reg. No U56/37595/2020
Dept. of Pharmacy
Faculty of Health Sciences
University of Nairobi

Dear Patrick,

RESEARCH PROPOSAL: PREVALENCE, RISK FACTORS AND MANAGEMENT OF NEUTROPENIA AMONG PAEDIATRIC CANCER PATIENTS WITH HEMATOLOGICAL MALIGNANCIES RECEIVING CHEMOTHERAPY AT KENYATTA NATIONAL HOSPITAL (P706/09/2022)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P706/09/2022.** The approval period is 20th December 2022 – 19th December 2023.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

APPENDIX 8: INSTITUTIONAL APPROVAL

KNH/R&P/FORM/01

KENYATTA NATIONAL HOSPITAL
P.O. Box 20723-00202 Nairobi

Tel.: 2726300/2726450/2726565
Research & Programs: Ext. 44705
Fax: 2725272
Email: knhresearch@gmail.com

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
   PATRICK MUTHINI JOHN
2. Email address: pmuthini123@gmail.com Tel No. 0710799447
3. Contact person (if different from PI).....
4. Email address: ..... Tel No. .....
5. Study Title
   PREVALENCE, RISK FACTORS AND MANAGEMENT OF NEUTROPENIA AMONG PAEDIATRIC CANCER PATIENTS WITH HEMATOLOGICAL MALIGNANCIES RECEIVING CHEMOTHERAPY AT KENYATTA NATIONAL HOSPITAL
6. Department where the study will be conducted ...PHARMACY DEPARTMENT
   (Please attach copy of Abstract)
7. Endorsed by Research Cordinator of Department where study will be conducted.
   Name: Dr. Were Irene Signature ..... Date 11/01/2023.
8. Endorsed by KNH Head of Department where study will be conducted.
   Name: DR A.R BIRICHI Signature ..... Date 11/01/2023
9. KNH UoN Ethics Research Committee approved study number P706/09/2022.
   (Please attach copy of ERC approval)
10. I PATRICK MUTHINI JOHN commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Medical Research.
    Signature..... Date 11/1/2023.
11. Study Registration number (Dept/Number/Year) Pharmacy 157 2023
    (To be completed by Medical Research Department)
    12 JAN 2023
12. Research and Program Stamp

All studies conducted at Kenyatta National Hospital **must** be registered with the Department of Medical Research and investigators **must commit** to share results with the hospital.

Plagiarism Report

Predictors and Management of Neutropenia Among Paediatric Patients With Haematological Malignancies at Kenyatta National Hospital

Endorsed
Dr. E.M. Guantai
Chair, DOPCPPP 28/11/2023.

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Patrick Muthini John	Peter N Karimi, PhD	Dr. E. M Guantai, PhD
Signature:	Signature:	Signature:
Date: 27/11/2023	Date 27/11/2023	Date: 28/11/2023